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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/600,564	11/07/2000	Florian Kern	KREISLER1089	5234

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EXAMINER
SHAHNAN SHAH, KHATOL S

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 09/09/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/600,564	KERN ET AL.	
	Examiner	Art Unit	
	Khatol S Shahnan-Shah	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-26* is/are pending in the application.

4a) Of the above claim(s) *22-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *14-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☒ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *21* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The Examiner of U.S. Patent application SN 09/600,564 has changed. In order to expedite the correlation of papers with the application please direct all future correspondence to Examiner Shahnan-Shah, Technology Center 1600.

2. Applicants' amendment of July 19, 2000 paper # 7 is acknowledged. Claims 1-13 were canceled and claims 14-26 were added.

3. Applicants' supplemental amendment of November 12, 2002 is acknowledged. Page 14 of the specification was amended to comply with sequence rule in response to a notice of Sequence Compliance dated October 15, 2002.

Election/Restrictions

4. Applicants' election with traverse of April 28, 2003 paper # 19 is acknowledged. Applicants provisionally elected Group I claims 14-21, which are drawn to a method for the identification of T-cell stimulating protein fragments.

The traversal is on the ground that the technical features of claim 22 are in fact, present in claims 23-26. Applicants requested that the examiner should withdraw the restriction requirement altogether.

The examiner clarified this issue on a telephonic interview with Ms. Jennifer Archer (attorney Kurt G. Briscoe's assistant) applicants' representative on July 31, 2003. Group I includes claims 14-21 not 14-22 as inadvertently was a typographical error made by the previous examiner in the restriction mailed 1/28/2003, paper # 18. The examiner respectfully apologizes if this caused any inconvenience. To clarify for the record: Group I, claims 14-21 are drawn to a method of identifying T- cell stimulating protein fragments, Group II claims 22-24

are drawn to a process for the preparation of a protein fragment and Group III claims 25-26 to a method of using a protein fragment. The three groups above lack the same or corresponding technical features.

The requirement is still deemed proper and is therefore made **FINAL.** Claims 22-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions.

5. Claims 14-21 are under consideration.

Priority

6. The disclosure is objected to because of the following informalities:

Priority statement is missing from specification:

This application filed under former 37 CFR 1.62 lacks the necessary reference to the prior application(s). A statement reading " This is a U.S.C. 371 of Application PCT/DE99/00175 filed on 1/15/1999 and claims priority to German applications No. 198 02174. 7., filed on 018/19/1998 and 198 34 932.7 filed on 7/28/1998 " should be entered following the title of the invention or as the first sentence of the specification. No English translations of German priority documents No. 198 02174. 7 and 198 34 932.7 have been received. A claim for priority under 35 U.S.C. 119 (a) -(d) (f) cannot be based on said applications, until proper corrections are made.

Drawings

7. The drawings are objected to by the Draftsperson under 37 CFR 1.84 or 1.152. See attached form PTO 948.

Information Disclosure Statement

8. The references cited in the PCT search report have been considered, but will not be listed on any patent resulted from this application because they were not provided on a separate list in compliance with 37 CFR 1.98 (a) (1). In order to have the references printed on such resulting patent, a separate listing on a PTO-1449 form, must be filed within the set period for reply to this office action.

Specification

9. The disclosure is objected to because of the following informalities:

The term "cytokin" is misspelled in the specification. The correct and accepted spelling is "cytokine".

Appropriate corrections are required.

Claim Objections

10. Claims 14-21 are objected to because of the following informalities: The term "cytokin" is misspelled in these claims. The correct and accepted spelling is "cytokine". Appropriate correction is required.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 14-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for the identification of 9 amino acid fragments of T-cell

stimulating protein, does not reasonably provide enablement for a method for the identification of other fragments of T-cell stimulating protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims of the instant application are drawn to a method for identification of T-cell stimulating fragments in general. Claim 14 also recite that these fragments comprise at least one protein fragment having a length of from 8-30 amino acids. The specification discloses amino acids sequences, which are each 9 and 15 amino acids in length (see page 14). There is no guidance provided as to other fragments or fragments comprising more than 9 or 15 amino acids. There is no guidance provided in the specification as how one would begin to choose "at least 8-30 amino acids".

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of prediction protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to

ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure.

One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. Multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims, which encompass all modifications and fragments because the specification does **not** disclose the following:

- other amino acid sequence for the claimed protein;
- the general tolerance to modification and extent of such tolerance;
- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;
- what fragments, if any, can be made which retain the biological activity if the intact protein; and
- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicant have **not** provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970). Without such guidance, the changes which can be made in the proteins structure and still maintain activity/utility is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen Inc v. Chugai Pharmaceutical Co Ltd. 927 F 2d 1200, 18 USPQ2d 1016 (Fed.Cir.1991) at 18 USPQ2d 1026-1027 and Exparte Forman, 230 U.S.P.Q. 546(Bd. Pat. App. & Int. 1986).

In view of all of the above, in view of the lack of predictability in the art, it is determined that it would require undue experimentation to make and use the invention commensurate in scope with the claims.

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

14. Claims 14-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 recites the limitation "the detected amino acid sequence" in step b. There is insufficient antecedent basis for this limitation in the claim.

Claim 14 is indefinite in reciting the abbreviation "MHC" in step f. The full name or explanation of the above mentioned abbreviation is required when it appears for the first time in the claim.

Claim 14, step f recites the phrases " which had been incubated with the T cells; characterized in that the incubation time is sufficiently long so that the protein fragment or fragments are sufficiently taken up by MHC molecules", " said taking up being sufficient when an unambiguous identification of stimulated T cell is possible" and "the incubation time with the fragment or fragments is sufficiently short". It is not clear what constitutes the metes and bounds of "sufficiently long", "sufficiently taken up" and "sufficiently short" in these steps,

Claim 19 recites the limitation "the patients to be subjected to therapy". There is insufficient antecedent basis for this limitation in the claim.

Claim 20, lines 2 - 3 recites the phrase " are derived from polycellular eukaryote, cells cell culture". It is not clear what applicants intend in reciting said phrase.

Claim 20 is vague and indefinite in reciting the term "i.e." in line 2.

Claim 21 is indefinite in reciting the abbreviation "TNF". The full name or explanation of the above mentioned abbreviation is required when it appears for the first time in the claim.

Art Rejections

15. Note: Prior to art rejection the examiner clarifies the priority date of this application. Since applicants have not complied to the foreign priority under 35 U.S.C. 119(a), (d) or (f). The priority date granted is 1/15/1999.

Claim Rejections - 35 USC § 102

16. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

17. Claims 14-21 are rejected under 35 U.S.C. 102(b) as being anticipated by Woitas et al. (Journal of Immunology of Immunology, Vol. 159, No. 2, pp. 1012-1018, 1997).

Claims are drawn to a method for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;
- synthesizing at least one protein fragment;
- incubating a suspension containing T-cells with the protein fragment;
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry;
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

Woitas et al. teach a method for identification of T-cell stimulating protein fragments comprising the following steps:

- detecting an amino acid sequence of an antigen;
- subdividing the amino acid sequence into fragments;(see page 1013, column 1, paragraphs 8-9)
- synthesizing at least one protein fragment; (see page 1013)

- incubating a suspension containing T-cells with the protein fragment; (see page 1013, column 2, paragraph 2)
- identifying an induced T-cell cytokine or activation of a marker by flow cytometry; (see page 1013, column 2, paragraph 3)
- assigning experimental runs in which T-cells have been stimulated and the stimulation has been recognized by a T-cell cytokine or an activation marker.

(see page 1013 , column 2, paragraph 3).

Woitas et al. describe the induction of CD30 and cytokines as a result of the HCV core protein or fragments thereof (see page 1013, column 1, paragraphs 8-9) acting on peripheral mononuclear cells of hepatitis patients (see abstract, pages 1013, 1014 and 1015). The peptides are incubated with cells (page 1013). The protein fragments essentially bound to MHC (page 1012). The T-cell cytokines such as, for example IL-2 and INFγ(see page 1014) undergo flow cytometry and therefore are identified as individual cell level (see page 1013 and 1014). The T-cell stimulation of both the protein fragments used are 25 amino acids long, and the control peptide is evaluated, i.e. protein fragments are allocated to T-cell stimulation (see figures 2 and 3 in page 1016 and page 1017). Woitas et al. teach both long and short incubation times. Woitas et al. teach long incubation time up to 40 hours (see page 13, column 2, paragraph 2) and short incubation time such as 30 minutes (see page 13, column 2, paragraph 3). The prior art anticipates the claimed invention.

Conclusion

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Khatol Shahnan-Shah whose telephone number is (703) 308-

8896. The examiner can normally be reached from 7:30 AM - 4 PM on Monday through Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le, can be reached on (703) 305-3399. The fax phone number for the organization where this application or proceeding is assigned to is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Khatol Shahnan-Shah, BS, Pharm, MS

Biotechnology Patent Examiner

Art Unit 1641

September 7, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

09/08/03